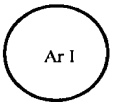
a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

98. (New) A compound according to claim 97, wherein Z is $-CO_2H$.

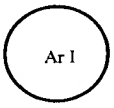
99. (New) A compound according to claim 97, wherein R' is hydrogen; and R" is lower alkyl.

100. (New) A compound according to claim 97, wherein



is optionally substituted azaheteroaryl.

101. (New) A compound according to claim 97, wherein



is 2-substituted-oxazol-4-yl.

**In the Abstract:**

Please delete the original Abstract and replace it with the Abstract attached to the end of this Amendment.

## Remarks

### I. Restriction and election requirements

Claims 1-24, 26-37, 47-48, 53-59, 61-66, 70 and 91-101 are pending in this application. Applicants have amended claim 55 to correct a typographical error in the spelling of the word "triglycerides." Applicants have also amended claim 1 and added new claims 97-101. Support for the new claims appears throughout the specification.

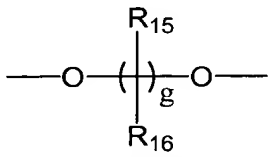
The Examiner maintained the restriction and election requirements of June 6, 2001. Applicants traverse the requirements for reasons already made of record. On

page 5 of the Office Action, the Examiner outlined the subject matter examined in this application. That outline parallels the following election made by the applicants:

Ar I: heterocycle, optionally substituted

Ar II: phenyl, optionally substituted

A:



B: a chemical bond

E: a chemical bond

Z: non-heterocycle

c: zero

d: zero

$R_1$-$R_4$: independently, hydrogen, halogen or alkyl.

Applicants assume that the Examiner's choice of the term "heterocycle" in making the restriction includes any group included with the definition of Ar I or Z that carries a non-carbocyclic ring, whether the heterocycle is a single ring or fused structure. Applicants also do not acquiesce in the Examiner's characterization of what core structures are or are not patentable over the art as discussed on pages 2-3 of the present Office Action. Applicants particularly do not acquiesce in the Examiner's comment of what constitutes the "key molecule of the invention" as discussed on page 3 of the Office Action. The patentability of applicants' invention is to be determined by reference to the claim as a whole as presented in the pending claims.

The Examiner agreed that claims 1-2, 8, 15, 26-31, 47-48, 53-59, 61-66, 91-92 and 96 read on the election, at least in part. New claims 97-101 also read on the election. Applicants assume that the Examiner has examined the full scope of the subject matter elected by applicants in response to the restriction requirement. Applicants respectfully request what effect, if any, the election of species by

applicants had on the scope of subject matter examined. Applicants particularly do not understand the Examiner's comment that "Since claims 1-2, 8, 15, 26-31, 47-48, 53-59, 61-66, 91-92, 96 link with other inventions they would be examined bearing in mind the subject matter as elected by the applicants only."

In light of the above, applicants respectfully request that the Examiner withdraw the requirements, or at least clarify the scope of subject matter being examined. Applicants respectfully request clarification of the requirements before deleting any subject matter from the claims.

**II. Abstract**

The Examiner objected to the abstract because of its length. Applicants have deleted the original Abstract and replaced it with the Abstract attached to the end of this Amendment. The new Abstract is of appropriate length, and applicants respectfully request that the Examiner withdraw the objection.

**III. Rejections under 35 U.S.C. § 112, second paragraph**

The Examiner rejected claims 1-2, 8, 15, 26-31, 47-48, 53-59, 61-66, 91-92 and 96 under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants address each of the Examiner's concerns below.

**A.** The Examiner stated that the terms "aryl," "fused aryl," "fused arylheterocycle" and "heteroaryl etc." as used in the definitions of Ar I and Ar II are indefinite because they do exactly and specifically tell the nature, size, number of heteroatoms and exact points of attachment to the "main core."

By reciting "etc." after the cited ring names, applicants assume that the Examiner's comments apply to all ring structures named in the definitions of Ar I and Ar II. The specification defines the term "aryl" at page 9, lines 10-13. Those skilled in the art understand that a "fused" ring is a ring having one or more of its sides in common with another ring. The specification defines the term "fused arylheterocyclyl" at page 10, lines 8-22, and "heteroaryl" at page 12, lines 15-32.

For terms in the definitions of Ar I and Ar II not specifically cited by the Examiner, the specification defines "fused arylcycloalkenyl" at page 9, lines 15-21,

"fused arylcycloalkyl" at page 9, lines 22-28, "fused arylheterocyclenyl" at page 9, line 29 to page 10, line 7, "fused heteroarylheterocyclyl" at page 14, lines 5-25, "fused heteroarylcycloalkenyl" at page 12, line 33 to page 13, line 9, "fused heteroarylcycloalkyl" at page 13, lines 10-24, "heteroarylheterocyclenyl" at page 13, line 25 to page 14, line 4 and "fused heteroarylheterocyclyl" at page 14, lines 5-25.

The definitions above contain information on the nature and size of the defined groups. With regard to the exact number of heteroatoms possible within the heterocyclic rings, the example listed in the definitions above make clear that the rings can contain one or more non-carbon atoms. An explicit restriction on that number is not necessary to meet the definiteness requirement. This is because one skilled in the art can determine whether a given group is a heterocyclic group, and the number of heteroatoms in a ring does not confuse this determination.

With regard to the Examiner's concerns that the claims do not recite exact points of attachment of the rings, an explicit restriction on the point of attachment also is not necessary to meet the definiteness requirement. The "floating" point of attachment illustrated in formula I represents a well accepted and well understood tool of illustration that has been in use in the scientific community for years. Indeed, the definitions of many of the ring structures discussed above explicitly note that the rings may be bonded to the rest of the compound through any atom of the ring capable of such bonding. If presented with a given compound, one skilled in the art would be able to determine whether the compound contains an Ar I or Ar II group as defined in the claims, and the particular point of attachment of such a group to the main core does not confuse this determination.

In light of the above, applicants respectfully request that the Examiner withdraw this rejection.

**B.** The Examiner stated that the phrase "optionally substituted" is indefinite because it does not convey exactly and specifically the number and point of attachment of substituents to the group being substituted.

With respect to the number of possible substituents, that can be evaluated as a function of the number of available positions on a ring that are available for

substitution. For example, a ring having two or three available positions available for substitution may be unsubstituted, substituted at only one of the positions, or substituted at both available positions. With regard to the exact point of attachment of a substituent to a group, the attachment can be made at any ring atom available for that substitution. If presented with a given compound, one skilled in the art can determine whether the given compound contains an Ar I or Ar II group having a substitution defined in the claims, and the particular point of attachment of substituents to the underlying ring groups does not confuse this determination.

In light of the above, applicants respectfully request that the Examiner withdraw this rejection.

**C.** The Examiner noted that no claim 25 exists in the originally-filed application. Applicants regret the typographical error in the original claims. In the listing of claims now pending in this application at the beginning of the Remarks above, applicants have made clear that there is no claim 25 pending in this application.

**D.** The Examiner stated that the term "radicals" in claims 27 and 28 is indefinite. The term "radicals" also appears in claim 1. Term "radical" simply refers to a particular "R" group recited in the claims. Since the definitions of the "R" groups in the claims is clear, applicants respectfully request that the Examiner withdraw this rejection.

**E.** The Examiner stated that the Preliminary Amendment "does not affirm the basis for the same" and that "there is not any specific mention of deletion or addition and its correlation either with the canceled claims or specification." Applicants do not understand those comments. The Preliminary Amendment filed by the applicants amends the specification and claims. The Examiner particularly stated that, for the amendment to claim 33, page 130, line 19, that location does not exist. The Preliminary Amendment identifies portions of the claims by referring to the claim number, and the page and line number of the application. Line 19 of page 130 of the specification recites "33. A compound according to claim 1 wherein

formula I as described by formula (Ia) below:" Applicants amended the claim to replace the word "as" with the word "is."

**F.** The Examiner stated that claims 91 and 92 were indefinite for reciting a ring system substituent, yet not specifying an exact point of attachment to the ring system.

The exact point of attachment of a substituent to a ring can be made at any ring atom available for that substitution. If presented with a given compound, one skilled in the art can determine whether the given compound contains a ring having a substitution defined in the claims. The particular point of attachment of substituents to the underlying ring group does not confuse this determination.

In light of the above, applicants respectfully request that the Examiner withdraw this rejection.

**G.** The Examiner argued that the expression "disease associated with . . . free fatty acids (FFA) or triglycerides" rendered claim 55 indefinite because the applicants "remain silent about the exact and specific nature of FFA as well as triglycerides."

Claim 55 recites a method according to claim 54, wherein the disease being treated is associated with a physiological detrimental blood level of insulin, glucose, free fatty acids or triglycerides. Those skilled in the art understand what triglycerides and free fatty acids are in the blood. Triglycerides comprise a proportion of fats in the diet, in the adipose tissue, and in the blood. With regard to free fatty acids, when a person eats fats, the body stores those fats in adipose or fat tissue, which then releases the fats into the bloodstream as free fatty acids. Applicants respectfully request that the Examiner withdraw this rejection.

**IV. Rejection under 35 U.S.C. § 112, first paragraph**

The Examiner rejected claims 1-2, 8, 15, 26-31, 47-48, 53-59, 61-66, 91-92 and 96 under 35 U.S.C. § 112, first paragraph, as non-enabled. In support of the rejection, the Examiner characterized and paraphrased the invention in a number of areas in the rejection. Applicants do not acquiesce in the Examiner's characterization of the invention or the manner in which it was paraphrased. The

claims as they are written define the invention. Applicants have attempted to address specific questions raised by the Examiner and to respond to arguments made by the Examiner in support the enablement rejection.

In making the enablement rejection, the Examiner acknowledged that the specification was enabling for the compounds in the treatment of Type II diabetes, but argued that the specification did not provide an enabling disclosure for other disorders such as cardiovascular conditions, hyperlipidemia, and hypertension. Because the Examiner acknowledged that the specification provides an enabling disclosure for at least one use of the compounds, claims 1-2, 8, 15, 26-31, 47-48, 53, 91-92 and 96 should not be included in this rejection. Those claims recite a compound or composition comprising the compound, not methods of use. As such, a single enabling use satisfies the utility part of the enablement requirement for those claims.

In light of the above, applicants substantively address the Examiner's rejection as it pertains to claims 54-59 and 61-66, which recite methods of use. After the Examiner's characterization of the invention on page 8 of the Office Action, the Examiner stated that the claims "remain silent about specific use method." Applicants do not understand that comment and request clarification.

The Examiner also commented that there are no known compounds of similar structure that have been demonstrated to treat the other conditions besides type II diabetes recited in the claims. Regardless of whether such compounds existed, however, the present disclosure provides a credible basis to support the treatments recited in the claims. The specification states that the claimed compounds are PPAR ligand receptor binders, and are useful as agonists or antagonists of the PPAR receptors. Page 4, lines 33-35. The specification further discusses actual binding assays useful for examining the action of the compounds. Pages 118-120.

The treatment in claim 54, of a disorder capable of being modulated by a compound having PPAR ligand binding activity, appears credible on its face, especially in light of the activity of the claimed compounds as PPAR ligand receptor binders. As stated in the specification, compounds having PPAR ligand binding

activity can be used, for example, in cell differentiation that produces lipid accumulating cells, and in the regulation of insulin sensitivity and blood glucose levels. Page 18, lines 9-11. Thus, the method of claim 55, which involves treating a disorder associated with detrimental levels of insulin, glucose, free fatty acids or triglycerides, also appears credible in light of the activity of the claimed compounds. Furthermore, given the underlying roles of insulin sensitivity and blood glucose levels in the hyperglycemia and hyperinsulinemia, it logically follows that the ability of the claimed compounds to regulate insulin sensitivity and blood glucose levels renders them candidates for the treatment of hyperglycemia (including diabetes and Type II diabetes), hyperinsulinemia and insulin resistance as recited in claims 56-59 and 61.

The specification at page 18, lines 14-15, indicates that the physiological disorders of macrophage differentiation, which leads to the formation of atherosclerotic plaques, can be modulated by compounds having PPAR ligand binding activity. Thus, the specification sets forth a credible basis for use of the claimed compounds, as PPAR ligand binders, in the treatment of cardiovascular conditions such as atherosclerosis as claimed in claims 62-63. For claim 64, use of the compounds in the treatment of hyperlipidemia logically follows from the disclosed effect of the compounds on cell differentiation and its production of lipid accumulating cells. Page 18, lines 10-11. Also as explained in the specification, obesity is an excessive accumulation of adipose tissue, and PPARγ is believed to play a central role in adipocyte gene expression and differentiation. Page 1, lines 23-24. Excess adipose tissue is associated with the development of serious medical conditions, for example, hypertension and hyperlipidemia obesity. Page 1, lines 26-27. Thus, a credible basis exists to believe that the compounds of the invention are useful in the treatment of hypertension and eating disorders as claimed in claims 65-66.

The Examiner also stated that there was no evidence of record that would enable one skilled in the art to identify a host who would be appropriate for the treatments recited in the claims. To the contrary, the recited conditions are well known to those skilled in the art, and those skilled in the art can identify hosts to be

treated for the recited disorders or who would otherwise pose sufficient risk factors to be subject to the treatments. To the extent that the Examiner disagrees, applicants respectfully request that the Examiner identify what disorders would not have been understood by those skilled in the art, or identify specific reasons why one skilled in the art could not identify a host having the disorders or having risk factors that would make the host appropriate for the claimed methods.

The Examiner also stated that the specification lacks any disclosure of doses of the compounds to treat the disorders recited in the claims. Applicants disagree. The specification states that a physician can determine the dosage of the compounds that would be most suitable for a particular patient. Page 122, lines 19-20. The specification lists example therapeutic doses of from 0.1 to 100 mM/day, 0.1 mg to 509 mg/kg of body weight per day, 10 mg to 50 mg/kg of body weight per day and 30 mg to 50 mg/kg of body weight per day. Page 122, lines 23-26.

The Examiner also commented that the specification does not present data showing a reduction or increase of a physiological disorder related to PPAR ligand binding activity in a patient. No such data should be required in this instance. The specification clearly states that the claimed compounds are PPAR ligand receptor binders, and are useful as agonists or antagonists of the PPAR receptors. Page 4, lines 33-35. The Examiner has not cited sufficient evidence or proposed sufficient arguments to doubt the credibility of that asserted utility. Furthermore, as discussed in detail above, the activity of the compounds provides a logical and credible scientific basis for concluding that they are useful for the treatment of the disorders recited in the method of treatment claims. The Examiner has not provided any evidence that would call those conclusions into question. The specification therefore need not disclose an actual clinical showing of the treatment of the disorders recited in the claims.

Lastly, in the last paragraph of page 10 and the first paragraph of page 11 of the Office Action, the Examiner repeated the opinion that the treatment of the various conditions recited in the claims is "unbelievable" and that the specification requires additional evidence demonstrating the utility of the compounds. As discussed

above, however, the treatment of the recited disorders is believable, is scientifically sound, and this rejection should be withdrawn.

**V. Rejections under 35 U.S.C. § 103(a)**

The Examiner rejected claims 1-2, 8, 15, 26-31, 47-48, 53-59, 61-66, 91-92 and 96 under 35 U.S.C. § 103(a) as unpatentable over WO 87/05510 to Youssefyeh et al. ("Youssefyeh") or U.S. Patent No. 4,794,188 to Musser et al. ("Musser"). Applicants respectfully traverse this rejection.

Youssefyeh discloses quinolinyl ether or thioether tetrazoles of Formula I shown on page 2 of the document. As indicated in Formula I of Youssefyeh, the compounds contain a tetrazolyl group, which corresponds in position to group "Z" in formula I of the present invention. As amended, group Z of the invention does not include a tetrazolyl group. Furthermore, the art would not have motivated one skilled in the art to replace the tetrazolyl group in Youssefyeh with a group within the present definition of group Z. The Examiner likewise has not suggested any reason why one skilled in the art would have been motivated to make such a modification to the Youssefyeh compounds. In particular, the Examiner's comments about a species rendering a genus obvious is not applicable to this situation, since Youssefyeh does not disclose compounds falling within the scope of the present claims.

Musser discloses quinolinyl ethers of formula I shown in col. 1 of the document. As indicated in Formula I of Musser, the compounds contain a group -Z-$(R)_{n'}$, which corresponds in position to group Z in the present claims, now that the definitions of B, E, c, and d in the present claims have been amended. The Musser group -Z-$(R)_{n'}$, with Z as an alkylene group, does not fall within any of the meanings of group Z in the present claims. Furthermore, the art would not have motivated one skilled in the art to replace the -Z-$(R)_{n'}$ group in Musser with a group that falls within the definition of group Z of the invention. The Examiner likewise has not suggested any reason why one skilled in the art would have been motivated to make such a modification to the Musser compounds. Once again, the Examiner's comments

about a species rendering a genus obvious is not applicable to this situation, since Musser does not disclose compounds falling within the scope of the present claims.

In light of the above, the present claim language satisfies the definiteness requirement, the specification adequately instructs those skilled in the art how to practice the invention, and the invention is patentable over the art. If there is any fee due in connection with the filing of this Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

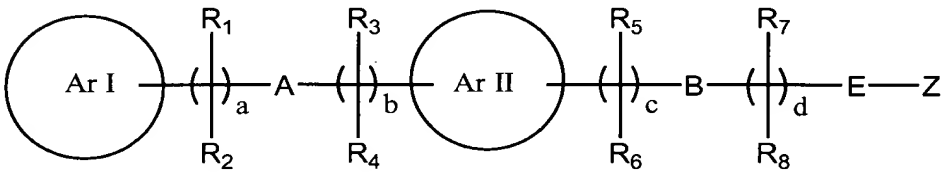
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: _____
Steven J. Scott
Reg. No. 43,911

Date: January 18, 2002

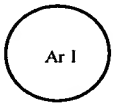
## Appendix Detailing Amendments to Application

1. (Twice Amended) A compound of formula (I)

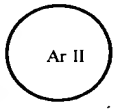



(I)

wherein:

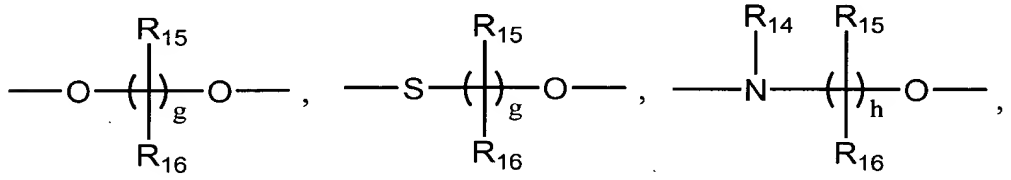


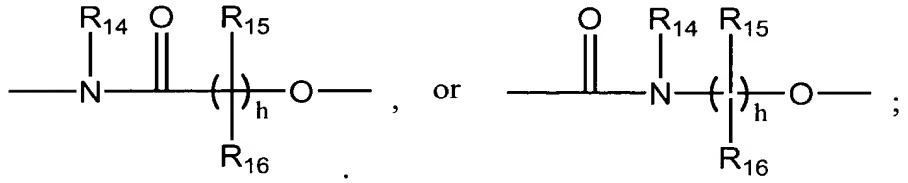

and




are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

A is -O-, -S-, -SO-, -$SO_2$-, -$NR_{13}$-, -C(O)-, -$N(R_{14})C(O)$-, -$C(O)N(R_{15})$-, -$N(R_{14})C(O)N(R_{15})$-, -$C(R_{14})$=N-, a chemical bond,




B and E are a chemical bond [is –O-, -S-, -$NR_{19}$-, a chemical bond, -C(O)-, -$N(R_{20})C(O)$-, or –$C(O)N(R_{20})$-;

E is a chemical bond or an ethylene group];

a is 0-6;

b is 0-4;

c is 0 [ -4 ];

d is 0 [ -6];

g is 1-5;

h is 1-4;

$R_1$, $R_3$, $R_5$ and $R_7$, are independently hydrogen, halogen, alkyl, carboxyl, alkoxycarbonyl or aralkyl;

$R_2$, $R_4$, $R_6$ and $R_8$, are independently $-(CH_2)_q-X$;

q is 0-3;

X is hydrogen, halogen, alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, carboxyl, alkoxycarbonyl, tetrazolyl, acyl, acylHNSO$_2$-, -SR$_{23}$, $Y^1Y^2N$- or $Y^3Y^4NCO$-;

$Y^1$ and $Y^2$ are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or one of $Y^1$ and $Y^2$ is hydrogen or alkyl and the other of $Y^1$ and $Y^2$ is acyl or aroyl;

$Y^3$ and $Y^4$ are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl;

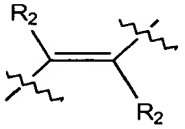
Z is $R_{21}O_2C$-, $R_{21}OC$-, cyclo-imide, -CN, $R_{21}O_2SHNCO$-, $R_{21}O_2SHN$-, $(R_{21})_2NCO$-, $R_{21}O$-, or 2,4-thiazolidinedionyl [, or tetrazolyl]; and

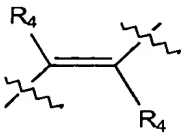
$R_{21}$ is independently hydrogen, alkyl, aryl, cycloalkyl, or aralkyl;

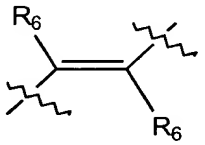
$R_{13}$ [, $R_{19}$] and $R_{23}$ are independently $R_{22}OC$-, $R_{22}NHOC$-, hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl;

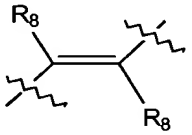
$R_{14}$, $R_{15}$, $R_{16}$ [and $R_{20}$] are independently hydrogen, alkyl, aralkyl, carbonyl, or alkoxycarbonyl;

or $R_{14}$, and $R_{15}$ taken together with the carbon and nitrogen atoms through which they are linked form a 5 or 6-membered azaheterocyclyl group; or

when a is 2-6, then at least one pair of vicinal $R_1$ radicals taken together with the carbon atoms to which the $R_1$ radicals are linked form a  group; or

when b is 2-4, then at least one pair of vicinal $R_3$ radicals taken together with the carbon atoms to which the $R_3$ radicals are linked form a  group; or

[when c is 2-4, then at least one pair of vicinal $R_5$ radicals taken together with the carbon atoms to which the $R_5$ radicals are linked form a  group; or

when d is 2-6, then at least one pair of vicinal $R_7$ radicals taken together with the carbon atoms to which the $R_7$ radicals are linked form a  group, or a 5-membered cycloalkyl group; or

when d is 2-6, then at least one pair of non-vicinal $R_7$ radicals taken together with the carbon atoms to which the $R_7$ radicals are linked form a 5-membered cycloalkyl group; or]

geminal $R_5$ and $R_6$ radicals taken together with the carbon atom through which these radicals are linked form a 5 membered cycloalkyl group; or

geminal $R_7$ and $R_8$ radicals taken together with the carbon atom through which these radicals are linked form a 5 membered cycloalkyl group; and

$R_{22}$ is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl; or

a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

55. (Amended) A method according to claim 54 wherein the disease is associated with a physiological detrimental blood level of insulin, glucose, free fatty acids [(FFA)], or triglycerides [triclycerides].